GLYCOGEN PHOSPHORYLASE INHIBITOR COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to glycogen phosphorylase inhibitor compounds, pharmaceutical compositions of these compounds, the use of these compounds or pharmaceutical compositions containing them in the treatment of diabetes, conditions associated with diabetes, and/or tissue ischemia including myocardial ischemia, and processes for making the compounds.

BACKGROUND OF THE INVENTION

[0002] Treatment of diabetes remains less than satisfactory. In addition, recently compiled data from the World Health Organization (WHO) show that approximately 150 million people have diabetes mellitus worldwide, and that this number may well double by the year 2025.

[0003] A number of drugs are available for the treatment of diabetes. These include injected insulin and drugs such as sulfonylureas, glipizide, tobutamide, acetohexamide, tolazimide, biguanides, and metformin (glucophage) which are ingested orally. Insulin self-injection is required in diabetic patients in which orally ingested drugs are not effective. Patients having Type 1 diabetes (also referred to as insulin dependent diabetes mellitus) are usually treated by self-injecting insulin. Patients suffering from Type 2 diabetes (also referred to as non-insulin dependent diabetes mellitus) are usually treated with a combination of diet, exercise, and an oral agent. When oral agents fail insulin may be prescribed. When diabetic drugs are taken orally usually multiple daily doses are often required.

[0004] Determination of the proper dosage of insulin requires frequent testing of the sugar in urine and/or blood. The administration of an excess dose of insulin generally causes hypoglycemia which has symptoms ranging from mild abnormalities in blood glucose to coma, or even death. Orally ingested drugs are likewise not without undesirable side effects. For example, such drugs can be ineffective in some patients and cause gastrointestinal disturbances or impair proper liver function in other individuals. There is a continuing need for drugs having fewer side effects and/or ones that succeed where others fail.

[0005] In Type 2 or non-insulin dependent diabetes mellitus, hepatic glucose production is an important target. The liver is the major regulator of plasma glucose levels in the fasting state. The rate of hepatic glucose production in Type 2 patients is typically significantly elevated when compared to normal (non-diabetic) individuals. For Type 2 diabetics, in the fed or postprandial state, the liver has a proportionately smaller role in the total plasma glucose supply, and hepatic glucose production is abnormally high.

[0006] The liver produces glucose by glycogenolysis (breakdown of the glucose polymer glycogen) and gluconeogenesis (synthesis of glucose from 2- and 3-carbon precursors). Glycogenolysis therefore is an important target for interruption of hepatic glucose production. There is some evidence to suggest that glycogenolysis may contribute to the inappropriate hepatic glucose output in Type 2 diabetic patients. Individuals having liver glycogen storage diseases such as Hers' disease or glycogen phosphorylase deficiency often display episodic hypoglycemia. Further, in normal post-absorptive humans up to about 75% of hepatic glucose production is estimated to result from glycogenolysis.

[0007] Glycogenolysis is catalyzed in liver, muscle, and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase. This enzyme cleaves the glycogen macromolecule to release glucose-1-phosphate and a shortened glycogen macromolecule.

[0008] Glycogen phosphorylase inhibitors include glucose and its analogs, caffeine and other purine analogs, cyclic amines with various substitutents, and indole-like compounds. These compounds and glycogen phosphorylase inhibitors in general have been postulated to be of potential use in the treatment of Type 2 diabetes by decreasing hepatic glucose production and lowering lycemia. Furthermore, we believe it maybe desirable that a glycogen phosphorylase inhibitor be sensitive to glucose concentrations in blood. Several different types of glycogen phoshorylase inhibitors have been reported. These include glucose and glucose analogs, caffeine and other purine analogs, indole compounds and acyl ureas.

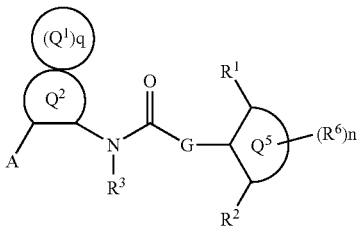
[0009] Accordingly, what is desired is a new compound and pharmaceutical composition thereof for the treatment of diabetes and/or conditions associated with diabetes.

SUMMARY OF THE INVENTION

[0010] The present invention provides a novel glycogen phosphorylase inhibitor compound and a pharmaceutical composition thereof that binds to at least one site of the glycogen phosphorylase enzyme. We believe that this novel glycogen phosphorylase inhibitor compound and a pharmaceutical composition thereof bind to the AMP allosteric binding site, and are glucose sensitive.

[0011] In one embodiment of the invention there is provided a novel compound of Formula 1 comprising:

Formula 1



[0012] a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof

[0013] wherein:

[0014] A is C(=O)NQ^{3}Q^4 or C(=O)OH;

[0015] Q^1 and Q^2 are fused together;

[0016] Q^1 is selected from the group consisting of (i) a 5- or 6-membered aromatic ring, (ii) a 5- or 6-membered cycloalkyl ring, (iii) a 5- or 6-membered heteroaromatic ring having at least one heteroatom selected from the group consisting of nitrogen, oxygen, or sulfur, and (iv) a 4- to